PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB 1729-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/50373	International filing date *(day/month/year)* 12.08.2003	Priority date *(day/month/year)* 14.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/00		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2004	18.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Cielen, E Telephone No. +31 70 340-4540

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50373

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-8 as originally filed

Claims, Numbers

1-7 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-7 (all partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5, 7 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 4-7 (all partially) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-7
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i Articles 5 and 6 PCT.

The application does not meet the requirements of Articles 5 and 6 PCT, because claims 1-7 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Claims 1-5 and 7 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the subject-matter in terms of the result to be achieved, namely "a NF-κB inhibitor" and "a specific NF-κB inhibitor". Such a definition is only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, such a formulation is not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of the chemical names of the compounds, namely the NF-κB inhibitors specifically mentioned in claim 6.

(b) In addition, present claims 4-7 relate to a very large number of possible compounds, namely "antibiotics". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, namely the antibiotics specifically mentioned in the description, p. 4, lines 20-25 (see also item **V.iv(d)**).

No International Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also item **V.i**).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for the use of the NF-κB inhibitors specified in claim 6 for the treatment of mastitis, optionally in combination with the antibiotics specifically mentioned in the description, p. 4, lines 20-25).

Claims 1-7 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D1: Journal of Dairy Science, 82(12), 2574-2581, 1999 (Bouchard)
D2: Biosis Abstract AN PREV200100325362 & J. Leukocyte Biol., 69(5), 815-824, 2001 (Zouki)
D3: WO-A-0056341
D4: Medline Abstract AN NLM5749697 & J. Am. Vet. Med. Assoc., 153(12), 1683-1687, 1968 (Newbould)

V.iii. Article 33(2) PCT.

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 mentions that it would be interesting to investigate the anti-inflammatory potential of substances which interfere with the activation of NF-κB in a model of mastitis (p. 2580, left-hand column, par. 1). Therefore, the subject-matter of claim 1 is not novel over D1.

V.iv. Article 33(3) PCT.

The problem to be solved by the present application is the provision of a medicament for the treatment of mastitis, while overcoming the disadvantages associated with the use of antibiotics (p. 1, lines 19-24). The proposed solution is the use of NF-κB inhibitors.

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-7 does not involve an inventive step in the sense of Article 33(3) PCT.

(a) Even if novelty could be restored, the presence of an inventive step would have to be demonstrated over D1, which clearly suggests the use of NF-κB inhibitors for the treatment of mastitis.

D1, which is considered to represent the most relevant state of the art, demonstrate that the iNOS inhibitor aminoguanidine can prevent NO release during mastitis and suggest a potential therapeutic value (Abstract; p. 2574, right-hand column, par. 1; p. 2577, right-hand column, par. 2-3; p. 2578, right-hand column, par. 2-3; p. 2579, right-hand column, par. 3; p. 2580, left-hand column, par. 1). From D2, it is known that aminoguanidine also interferes with NF-κB signalling, by blocking accumulation of NF-κB in leukocytes (abstract). D1 further mentions that it would be interesting to investigate the anti-inflammatory potential of substances which interfere with the activation of NF-κB in a model of mastitis (see item **V.iii**).

The subject-matter of claim 6 differs herefrom in that specific NF-κB inhibitors are used for the same therapeutic purpose.

The problem to be solved by the present invention may therefore be regarded as the provision of specific NF-κB inhibitors for the treatment of mastitis.

Since the compounds of the present invention appear merely to be alternative (known - as also recognised by the Applicant in the description p. 1, line 35 - p. 2, line 13) NF-κB inhibitors, without any documented unexpected technical effect, the invention is regarded as obvious and cannot be considered as inventive.

(b) In addition, the compounds belong to very different classes of chemical compounds. The description provides only experimental data for 15d-PGJ2 and gliotoxin.

At present, it appears therefore questionable that all the compounds of claim 1 are a solution to the problem underlying the application. The presence of an inventive step can only be recognised for problems which have been solved by all claimed variants.

© The application also lacks an inventive step based on document D3, which discloses the use of a NF-κB inhibitor for the treatment of bacterial-mediated disorders, e.g. *Staphylococcus aureus* (p. 6, par. 6-8; p. 11, par. 2-4). The compounds can be used for veterinary treatments (p. 9, par. 2-3). It is generally known that mastitis is due to *Staphylococcus aureus* infections (as demonstrated by e.g. D4, which is one of the numerous documents disclosing this link). It was therefore obvious for the person skilled in the art, knowing from D3 that NF-κB inhibitors are useful for the treatment of *S. aureus* infections and from D4 that mastitis is due to such infections, to at least try to treat mastitis with NF-κB inhibitors with a reasonable expectation of success, both for chronic and acute mastitis, since the same microorganisms cause both variants.

(d) As far as the coadministration of NF-κB inhibitors with antibiotics is concerned, an inventive step can only be recognised provided a surprising or unexpected effect, e.g. synergy, has been demonstrated, because both NF-κB inhibitors (D1) and antibiotics

(general knowledge) are separately known for their activity in the treatment of mastitis. It is to be noted that additive effects do not account for the presence of an inventive step, since a skilled person would expect some beneficial effect of the combinations as claimed, based on the separate activities of both actives.